

## Functional group dependence of the acid catalyzed ring opening of biomass derived furan rings: an experimental and theoretical study†

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We describe studies of Brønsted acid catalyzed ring opening of substituted furans contained within biomass derived C<sub>8</sub>- and C<sub>9</sub>-molecules. Ring opening occurs homogeneously under relatively mild conditions of 80 °C using catalytic hydrochloric acid. In the case of 4-(5-methyl-2-furyl)-2-butanone (**1a**), the reaction proceeds to a single product in up to 92% yield after 24 hours. For 4-(2-furanyl)-2-butanone (**1b**) and 4-(5-hydroxymethyl)-2-furanyl-2-butanone (**1c**), however, multiple products are observed, illustrating the significant influence of furan ring substituents on the reactivity of this class of compounds. The generality of these reaction pathways was tested using several other similar substrates. Kinetics experiments indicate that ring opening of **1a** occurs *via* specific acid catalysis, and computations elucidate the effect of initial protonation on the reaction pathway. Calculated pK<sub>a</sub> values were calibrated against experimentally measured values and are consistent with observed reactivities. Inclusion of explicit, hydrogen-bonded water molecules in addition to the SMD solvent model is necessary when studying protonation of alcohol and ketone groups.

### Introduction

Conversion of non-food based plant biomass into transportation fuels and chemical feedstocks has recently received a great deal of attention.<sup>1</sup> To achieve this, several challenging chemical transformations must be performed, including the breakdown of lignocellulose, followed by (in the case of high energy density fuel synthesis) lengthening of carbon chains within the resulting sugars, and then extensive deoxygenation and hydrogenation of the resulting products.<sup>1</sup> Current technologies to convert biomass into fuels include gasification followed by Fischer–Tropsch synthesis and pyrolysis to bio-oil.<sup>1–3</sup> Unfortunately, these processes are generally non-selective and require high temperatures as well as initial oxidation of the biomass.

Cellulosic biomass can be hydrolyzed under mild conditions yielding five and six carbon sugars as products.<sup>4</sup> Subsequent

dehydration of these sugars affords products containing furan and aldehyde moieties, including furfural, methyl furfural, dimethyl furan and hydroxymethyl furfural (HMF).<sup>4,5</sup> An aldol condensation between these furfural products and acetone selectively yields compounds containing eight or nine carbon atoms<sup>6</sup> that are suitable for upgrading to diesel fuels. These and similar compounds can be ring opened, deoxygenated and hydrogenated by a variety of heterogeneous metal catalysts at high temperatures and high hydrogen pressures to provide linear alkanes suitable for use as fuels.<sup>1,3,7</sup>

The petrochemical industry has studied the conversion of crude oil into fuels and synthetic feedstocks for more than a century,<sup>8</sup> resulting in an enormous body of knowledge and understanding of the processes involved. In contrast, the understanding of biomass conversion to hydrocarbons is comparatively limited. Furan rings, for example, are ubiquitous in cellulose derived fuel precursors, and opening these rings is necessary for production of the desired linear alkanes.<sup>1</sup> Many of the conversion processes to date view the furan ring simply as an aromatic to be hydrogenated. Ring opening the resulting tetrahydrofuran then requires comparatively extreme conditions, as illustrated in Path A of Scheme 1,<sup>1,3,7</sup> or stoichiometric coupling with other reagents.<sup>9</sup> Species **1** in this case represents the result of a commonly adopted approach in which the furan ring and the ketone are both hydrogenated. High temperature, heterogeneous processes have been shown to be effective for furan ring opening reactions; however wide product distributions

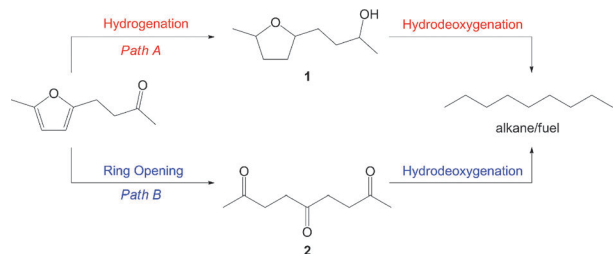
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Scheme 1

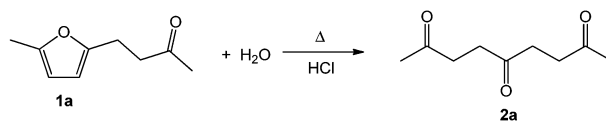
and fragmentation of the carbon backbone is often observed.<sup>7,10</sup> Development of selective processes that occur at lower temperature and pressures will reduce capital and process costs, making the conversion of biomass into fuels more economically viable. Furan ring opening reactions using metal catalysts and stoichiometric oxidants have also been studied in detail,<sup>11</sup> as has Pt-catalyzed electrolytic furan ring opening,<sup>12</sup> but these approaches are impractical for fuel production.

In contrast, the direct ring opening of the furan ring is a good *first* step since the acid catalyzed ring opening occurs readily under relatively mild conditions (Path B, Scheme 1). Acid catalyzed furan ring opening has been known for some time,<sup>13,14</sup> but use of this pathway for hydrocarbon production has not been considered to any great extent and has received relatively little detailed mechanistic study, especially with respect to biomass derived substrates. This enables a lower temperature, chemically selective approach that utilizes inexpensive catalysts for the upgrading of biomass, which is very desirable. Following acid catalyzed furan ring opening, the biomass could be treated using the same hydrodeoxygenation processes required in Path A. Furthermore, development of a detailed understanding of the mechanism and selectivity of furan ring opening in biomass derived substrates will enable design of improved processes and better catalysts. We will report on more recent results pertaining to the conversion of species such as **2** below into hydrocarbons in due course.<sup>15</sup>

Herein, Brønsted acid catalyzed ring opening of biomass derived molecules containing eight and nine carbon atoms are presented. Ring opening occurs under mild conditions (80–100 °C) using catalytic HCl. In the case of 4-(5-methyl-2-furyl)-2-butanone (**1a**), the reaction proceeds quantitatively to a single product. For 4-(2-furanyl)-2-butanone (**1b**) only slight decomposition is observed while for 4-(5-hydroxymethyl)-2-furanyl-2-butanone (**1c**) multiple products are observed, indicating the significant effect of substituents on the reactivity of this class of compounds. The  $\alpha,\beta$  unsaturated precursors **3a–c** were also tested for ring opening, but only slight decomposition was observed. DFT calculations along with kinetics experiments indicate a specific acid catalysis mechanism and show that the location of initial protonation influences the overall product distribution.

## Results

Ring opening studies began with the nine-carbon containing species 4-(5-methyl-2-furyl)-2-butanone (**1a**), shown in Scheme 2. **1a** was obtained *via* aldol condensation between 5-methylfurfural (a product of cellulose hydrolysis and dehydration<sup>5</sup>) and acetone,<sup>6,16</sup> followed by reduction of the exocyclic unsaturation



Scheme 2

with magnesium.<sup>17</sup> Heating **1a** at 100 °C with excess HCl has been reported to give 2,5,8 nonanetrione (**2a**) in high yield,<sup>18</sup> so this reaction served as a starting point for development of a catalytic process under milder conditions. Initial test reactions using a ten-fold excess of HCl at 100 °C over 3 hours did show clean conversion to **2a** in 93% yield determined by <sup>1</sup>H NMR spectroscopy. Following these results, milder conditions with lower temperatures and catalytic amounts of HCl were investigated. **1a** is only slightly soluble in water, so five different mixtures of water and water-miscible organic solvent (1 : 1 by volume) were also tested. Control reactions showed no reaction after heating **1a** in the absence of catalyst at 80 °C for 48 hours. As illustrated in Table 1, good yields of **2a** were observed in several cases after 24 hours, even after heating at only 60 °C, and no other products were observed. Optimal conversion to **2a** was observed at higher temperatures and while all the organic solvent mixtures made **1a** soluble in the reaction mixture, conversion to **2a** was not greatly improved relative to pure water as the reaction solvent at 100 °C.<sup>19</sup> Throughout the course of these reactions, no intermediates were observed; only starting material and the final product were detected by <sup>1</sup>H NMR spectroscopy and GC-MS. When this reaction was performed on a half gram scale, **2a** was obtained in 85% isolated yield.

Other Brønsted acids were also tested as catalysts for this reaction, as shown in Table 2. The strong Brønsted acids HNO<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub> and CF<sub>3</sub>COOH all give yields of **2a** similar to those observed when HCl is used. In contrast, the weaker organic acids, acetic acid and formic acid, give only 1.4% and 4% yields of **2a**, respectively after 24 hours. A variety of metal salts were also tested as catalysts, but none were as effective as the strong Brønsted acids discussed here.<sup>20</sup>

Several experiments were performed to further probe the mechanism of the ring opening reactions. Compound **1a** was heated in solutions buffered to a pH of 3 with a 1 : 1 ratio of HCl and KCl, with buffer concentrations of 0.2 M, 0.16 M, and 0.12 M. All three solutions gave the same yield of ring opened **2a** after heating at 80 °C for 24 hours, despite nearly halving the buffer concentration. This is consistent with a specific acid catalysis mechanism in which the rate of catalysis depends solely on the concentration of hydronium ions in solution. Compound **1a** was also heated for 24 hours at 80 °C

**Table 1** Yield of ring opened product **2a** from heating **1a** for 24 hours in various solvent systems with 10 mol% HCl

Solvent <sup>a</sup>	60 °C	70 °C	80 °C
Water : acetone	12%	25%	59%
Water : acetonitrile	18%	43%	77%
Water : methanol	29%	59%	94%
Water : ethanol	14%	25%	50%
Water : isopropanol	11%	22%	41%
Water	44%	91%	87%

<sup>a</sup> Solvent mixtures are 1 : 1 water : organic solvent by volume.

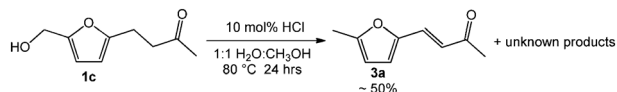
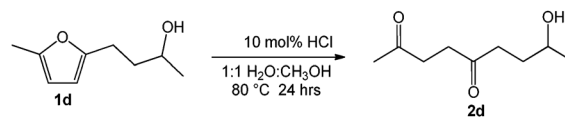
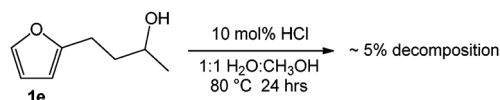
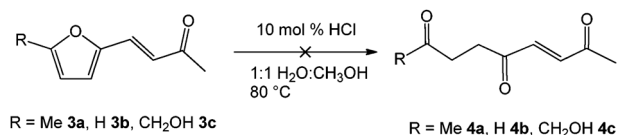
**Table 2** Yield of ring opened product **2a** using 10 mol% catalyst in 1 : 1 water : methanol as solvent

Acid	Yield of <b>2a</b>
HCl	94%
HNO <sub>3</sub>	77%
H <sub>2</sub> SO <sub>4</sub>	84%
CH <sub>3</sub> COOH	1.4%
HCOOH	4%
CF <sub>3</sub> COOH	77%

in a 1 : 1 mixture of CD<sub>3</sub>OD and D<sub>2</sub>O with 10 mol% of (proteo) hydrochloric acid as a catalyst. After 24 hours, the observed yield of **2a** was only 45%, likely due to the lower acidity of D<sub>2</sub>O solutions.<sup>21</sup> <sup>1</sup>H and <sup>13</sup>C NMR analysis of the product indicate that deuterium is incorporated predominantly in the methylene positions of the product, though some deuteration of the methyl groups is also observed.

A recent study has highlighted the effect of different furan ring substituents on observed reactivity,<sup>22</sup> so the ring opening of other substrates was also examined here. The eight carbon compound 4-(2-furanyl)-2-butanone, **1b**, was prepared using the same method as for **1a** using furfural and acetone.<sup>16,17</sup> Approximately 5–10% decomposition to unknown products is observed upon heating **1b** at 80 °C with 10 mol% of HCl in a 1 : 1 water : methanol mixture (Scheme 3). In contrast, heating **1b** in a 1 : 1 water–acetone mixture yields a nineteen-carbon product **2b** in 90% yield by <sup>1</sup>H NMR spectroscopy, as shown in Scheme 4. Running the reaction in D<sub>2</sub>O and acetone-*d*<sub>6</sub> gives the same product, but with incorporation of *ca.* 10 deuterium atoms: based on <sup>1</sup>H NMR analysis, the methyl groups between the furan rings are completely deuterated while significant amounts of deuterium are present in the ketone methyl groups as well. Thus, **2b** appears to be the product of condensation of two molecules of **1b** and one acetone molecule (Scheme 4). No reaction is observed when **1b** is heated in water : acetone solvent without added acid. Heating **1b** in other solvent mixtures gave complex mixtures of unknown products.

A third biomass derived substrate 4-(5-hydroxymethyl)-2-furanyl-2-butanone, **1c**, was prepared from HMF and acetone,<sup>16</sup> followed by reduction of the exocyclic unsaturation with magnesium.<sup>17</sup> Upon heating **1c** in water or organic solvent mixtures, several products are observed by <sup>1</sup>H NMR spectroscopy and GC-MS. One major product (*ca.* 50%) is the partially deoxygenated  $\alpha,\beta$ -unsaturated compound **3a** (Scheme 5). Column chromatography yielded complex mixtures of other unidentified products. The absence of furan peaks in the <sup>1</sup>H NMR spectra of some of these fractions suggests that

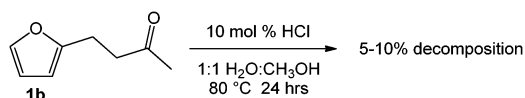
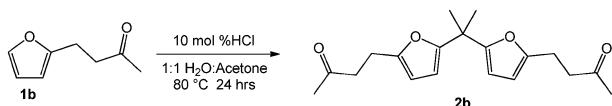
**Scheme 5****Scheme 6****Scheme 7****Scheme 8**

some ring opening does occur, however. No reaction is observed when **1c** is heated in water : acetone solvent without added acid.

Sodium borohydride reduction of **1a** yielded the ketone reduced compound, 4-(5-methylfuran-2-yl)butan-2-ol (**1d**). Heating **1d** in the presence of HCl gave the ring opened diketone alcohol **2d** quantitatively as determined by <sup>1</sup>H NMR spectroscopy (Scheme 6). Sodium borohydride reduction of **1b** gave 4-(furan-2-yl)butan-2-ol (**1e**), and slight decomposition was observed when **1e** was heated with HCl (Scheme 7). Thus, reduction of the ketone to the alcohol does not appear to affect the reactivity with respect to furan ring opening. Ring opening of the  $\alpha,\beta$  unsaturated products **3a–c** was also investigated as summarized in Scheme 8. Upon heating compounds **3a–c** in 1 : 1 water : methanol at 80 °C, some darkening of the reaction mixture occurred, but no ring opening is observed by NMR after 24 hours.<sup>23</sup> Additionally, no condensation is observed when **3b** is heated in acetone, so the reaction shown in Scheme 4 is unique to the hydrogenated compound **1b**.

## Computational results

The thermodynamics of the reactions discussed above were investigated *via* DFT calculations using the B3LYP<sup>24</sup> density functional and 6-311 + G(d) basis set or the high-level CBS-QB3<sup>25</sup> composite method. The conductor-like polarizable continuum model (CPCM) was used to approximate the effects of solvation.<sup>26</sup> Natural atomic charges<sup>27</sup> were computed with the NBO 3.1 program as implemented in Gaussian 09.<sup>28</sup> The method of Liptak *et al.* was used, with a few modifications (*vide infra*) to calculate *pK<sub>a</sub>* values in solution.<sup>28</sup> Although ring opening reactions were carried out at 80 °C experimentally, free energies were computed at 25 °C for two reasons: first,

**Scheme 3****Scheme 4**

**Table 3** Thermodynamics of overall ring opening reaction, calculated using the CPCM solvation model at 298 K

Reaction	$\Delta G^\circ$ (kcal mol <sup>-1</sup> )		
	B3LYP/6-311+G(d)	CBS-QB3	CBS-QB3 (80 °C)
<b>1a</b> + H <sub>2</sub> O → <b>2a</b>	-4.92	1.65	3.34
<b>1b</b> + H <sub>2</sub> O → <b>2b</b> *	-2.03	3.45	5.11
<b>1c</b> + H <sub>2</sub> O → <b>2c</b>	-4.44	0.28	2.03
<b>1d</b> + H <sub>2</sub> O → <b>2d</b>	-4.88	0.77	2.36
<b>1e</b> + H <sub>2</sub> O → <b>2e</b>	-2.88	2.90	4.48
<b>3a</b> + H <sub>2</sub> O → <b>4a</b>	2.88	5.61	7.10
<b>3b</b> + H <sub>2</sub> O → <b>4b</b>	4.34	7.24	8.76
<b>3c</b> + H <sub>2</sub> O → <b>4c</b>	8.27	3.95	5.55

Liptak's method incorporates an empirical proton solvation free energy measured at 25 °C,<sup>29</sup> and second, free energies for overall ring opening (Table 3) increase by no more than 1.8 kcal mol<sup>-1</sup> at 80 °C relative to those calculated at 25 °C. All calculations were performed using the Gaussian 09 program.<sup>27</sup>

First, the overall thermodynamics of furan ring opening were examined. Structures of compounds **1a–e**, **2a**, **2b**\*, **2c–e**, **3a–c** and **4a–c** were first optimized in the gas phase (where **2b**\*, **2c**, and **2e** are the ring opened products of furans **1b**, **1c**, and **1e**, respectively<sup>20</sup>) followed by re-optimization using the CPCM solvent model (Table 3). With B3LYP/6-311+G(d), ring opening of **1a–e** to give the corresponding triketones is exergonic by 2.03 to 4.92 kcal mol<sup>-1</sup>. In contrast, ring opening of the  $\alpha,\beta$  unsaturated substrates **3a–c** is endergonic by 2.88 to 8.27 kcal mol<sup>-1</sup>. This is consistent with the experimentally observed reactivity: the hydrogenated substrates **1a–c** ring open or decompose slightly under the experimental conditions whereas the  $\alpha,\beta$  unsaturated substrates **3a–c** do not. Calculations with the CBS-QB3 method give somewhat different results, however. Ring opening of **1a–e** is slightly endergonic (0.28 to 2.90 kcal mol<sup>-1</sup>) while ring opening of compounds **3a–c** is even more unfavorable (3.95 to 7.24 kcal mol<sup>-1</sup>). In all cases, the ring opening is more endergonic with CBS-QB3 relative to B3LYP, with the exception of **3c** (8.27 (B3LYP) vs. 3.95 (CBS-QB3) kcal mol<sup>-1</sup>): this anomaly arises from enhanced solvent stabilization of **3c** with B3LYP relative to the other furans and ring opened products.<sup>20</sup> Despite the difference in absolute energies between the two methods, the qualitative result is the same: ring opening of the  $\alpha,\beta$  unsaturated substrates is less favored thermodynamically.

Next,  $pK_a$  values were calculated for select carbon and oxygen atoms of compounds **1a–e** and **3a–c**. In Liptak's method,<sup>28</sup>  $pK_a$ s are calculated with the CBS-QB3 composite method and CPCM solvent model using a thermodynamic cycle approach involving gas phase (CBS-QB3) acid dissociation ( $HA \rightarrow A^- + H^+$ ) and solvation (CPCM). However, whereas Liptak's analysis is limited to dissociation of neutral phenols to their anionic conjugate bases ( $HA \rightarrow A^- + H^+$ ), the  $pK_a$  values in the present work correspond to dissociation of protonated furans to their neutral conjugate bases ( $BH^+ \rightarrow B + H^+$ ). Due to this disparity, the solvent model and level of theory for solvation free energies were recalibrated against the experimental  $pK_a$  of 2,5-di-*tert*-butyl furan (Table 4).<sup>30</sup> In addition to the methods used for ring opening thermodynamics (CBS-QB3 and B3LYP/6-311+G(d) with CPCM solvation), Truhlar's universal SMD solvation model was employed along with three methods

**Table 4** Calibration of computational model for solvation free energies within  $pK_a$  calculations as a difference ( $\Delta pK_a$ ) between calculated and experimentally observed  $pK_a$  of 2,5 di-*tert*-butylfuran. Values correspond to protonation at the tertiary carbon

Method	Solvent model	$pK_a$	$\Delta pK_a$
Experimental value	—	-10.0	—
CBS-QB3	CPCM	-13.1	-3.1
CBS-QB3	SMD	-7.5	2.5
B3LYP/6-311+G(d)	CPCM	-11.1	-1.1
HF/6-31G(d)	SMD	-4.9	5.1
HF/6-31G(d)	CPCM	-10.6	-0.6
B3LYP/6-31G(d)	SMD	-5.8	4.2
B3LYP/6-31G(d)	CPCM	-11.3	-1.3
M05-2X/6-31G(d)	SMD	-6.2	3.8
M05-2X/6-31G(d)	CPCM	-11.5	-1.5

over which the model was optimized (B3LYP/6-31G(d), M05-2X/6-31G(d), and HF/6-31G(d)).<sup>31</sup> The most accurate result relative to the experimental value was obtained for HF/6-31G(d), the simplest method in the calibration set, in conjunction with CPCM ( $pK_a = -10.6$ ). This result is not particularly surprising, given that the CPCM solvent cavities were optimized for HF and small basis sets.<sup>25,28</sup> Furthermore, Liptak<sup>28</sup> found solvation free energies at this level of theory (CPCM/HF/6-31G(d)) to also yield the most accurate  $pK_a$ s of substituted phenols, suggesting that the best method for CPCM solvation within Liptak's method may be insensitive to the nature of the chemistry (protonation of neutral species vs. dissociation of acids) and identity of reagents (furans vs. phenols).

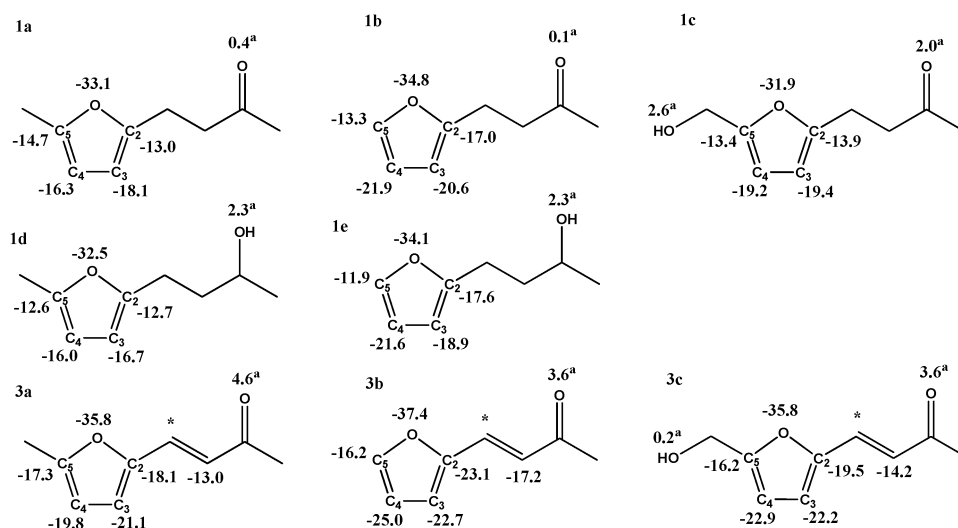
Use of a single experimental reference  $pK_a$  value is sufficient for this study for several reasons. First, the differences between calculated  $pK_a$  values of **1a–e** and **3a–c** using either CPCM/HF/6-31G(d) or CPCM/B3LYP/6-311+G(d) solvation energies are not drastic, with most values differing by no more than 4  $pK_a$  units.<sup>20</sup> Additionally, the latter of the two above methods gave the second most accurate  $pK_a$  of 2,5-di-*tert*-butyl furan (Table 4). Finally, the most acidic site of each molecule is in the same position regardless of the method used.<sup>20</sup> This illustrates the difficulty of calculating accurate  $pK_a$  values, and more extensive experimental and theoretical study of protonation of furan derivatives would be of value.

In terms of solvent model, SMD gives less accurate  $pK_a$  values than CPCM, even though the former was found to yield more accurate solvation free energies.<sup>30</sup> Whether or not this finding is indicative of deficiencies in Truhlar's SMD method is unclear, however, particularly given the scarcity of experimental  $pK_a$  data for furans. Nevertheless, CPCM/HF/6-31G(d) solvation energies will be used for most of the  $pK_a$  calculations in this work.

The  $pK_a$  values for protonation of select atoms within furans **1a–e** and **3a–c** are shown in Scheme 9. For **1a**, the most basic site of the furan ring is the carbon atom in the 2 position with a calculated  $pK_a$  of -13.0. This calculated value is close to the experimental  $pK_a$  value of -10.01 for 2,5-di-*tert*-butyl furan,<sup>29</sup> which has a very similar furan moiety. The remaining furan carbons are only slightly less basic with  $pK_a$  values ranging from -14.7 to -18.1. The furan oxygen is much less basic with a  $pK_a$  of -33.1.

Initially, we calculated that the ketone oxygen of **1a** has a  $pK_a$  value of -18.8. This was surprisingly different from the experimentally measured  $pK_a$  of protonated acetone, which has

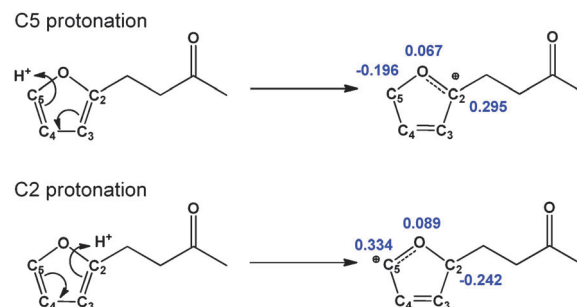




**Scheme 9** Calculated  $pK_a$  values for dissociation of a proton from the conjugate acids of substrates **1a-e** and **3a-c** ( $HA^+ \rightarrow A + H^+$ ). \*Denotes proton migration during geometry optimization, preventing calculation of a  $pK_a$  value for that atom. <sup>a</sup>Denotes an explicit water molecule was added and SMD/HF/6-31G(d) solvation free energies are used in place of CPCM/HF/6-31G(d) during calculation of the  $pK_a$  value.

a  $pK_a$  between  $-2$  and  $-3$ .<sup>32</sup> Our computational method gave a  $pK_a$  of  $-17.6$  for protonated acetone, almost 15–16  $pK_a$  units less basic than the experimental value. This suggests a deficiency in the method, and so the effect of an explicit water molecule hydrogen bonded to the protonated carbonyl group was tested.<sup>19</sup> For acetone, addition of just one explicit water molecule yields a calculated  $pK_a$  of 8.6, a value closer to the experimental value but significantly more basic than the measured value. Further improvement is found when SMD/HF/6-31G(d) solvation free energies are used in place of CPCM/HF/6-31G(d) values, giving a calculated  $pK_a$  of 1.8. This trend is also observed for **1a**, where the calculated  $pK_a$  goes from  $-18.8$  to 7.6 upon addition of a water molecule, and 7.6 to 0.4 on switching to SMD solvation. This behaviour is in contrast to furan ring protonation (Table 4), in which CPCM gives more accurate  $pK_a$ s than SMD. Since this trend is also found for the protonated carbonyl and hydroxyl groups of the remaining substrates,<sup>19</sup>  $pK_a$ s reported for these groups will correspond to deprotonation with an explicitly hydrogen-bonded water (FuranH<sup>+</sup> + H<sub>2</sub>O → Furan + H<sub>3</sub>O<sup>+</sup>) with SMD solvation, unless otherwise stated (Scheme 9). These considerations do not seem as important for the furan ring, however, where the calculated  $pK_a$  values appear to be in good agreement with experiment without explicit water molecules added. While use of different solvation models for different functional groups in the same substrate may seem problematic, it is appropriate in this case for two reasons. First, this dual methodology yields  $pK_a$ s close to expected experimental values (see above) and second, even with CPCM solvation, the hydroxyl and carbonyl groups remain the most basic sites for each substrate.<sup>19</sup> Replacing the electron-donating furyl methyl group of **1a** with a proton gives **1b**. The comparatively electron withdrawing proton makes the furan ring carbons within **1b** less basic than those of **1a** by 2–6  $pK_a$  units with the exception of C5, which is the most basic site on **1b**. Notably, protonation at C5 followed by geometry optimization yields a tertiary carbocation with the positive charge localized on the C2 carbon *via* rearrangement of the

ring  $\pi$ -electrons, as shown in Scheme 10. This was confirmed by computing CPCM/B3LYP/6-311+G(d) natural atomic charges for both protonated and neutral **1b**. While C5 protonation results in a decrease of positive charge on C5 relative to **1b** ( $\Delta q = -0.196$ ; Scheme 10), the positive charge increases on both C2 and O by 0.295 and 0.067 units, respectively. In contrast, initial protonation at the C2 carbon followed by geometry optimization gives a comparatively less stable secondary carbocation with the positive charge located on the C5 carbon (Scheme 10). Once again, the positive charge decreases at the site of protonation (C2) by  $-0.242$  units and increases on C5 and O by 0.334 and 0.089 units, respectively (Scheme 10); this increase is greater than that on C2 and O upon C5 protonation, implying that C2 protonation gives a less stable carbocation. These differences in carbocation stability account for the relatively large difference in  $pK_a$  values calculated for C2 ( $-17.0$ ) and C5 ( $-13.3$ ) in **1b**; the difference in  $pK_a$  value is much smaller in **1a** where tertiary carbocations are obtained *via* protonation at C2 or C5. The  $pK_a$ s of the furan and ketone oxygen atoms do not differ substantially from those in **1a**. As seen in **1a**, the calculated



**Scheme 10** Rearrangement of  $\pi$  electrons upon protonation of **1b** at the 2 and 5 position of the furan ring. Values of  $\Delta q$ , the difference in natural atomic charges between protonated and unprotonated **1b**, are highlighted in blue.

$pK_a$  of the carbonyl oxygen in **1b** increases from  $-18.9$  to  $0.1$  upon addition of an explicit water molecule and use of SMD solvation.

The condensation reaction between **1b** and acetone (Scheme 4) is consistent with the calculated  $pK_a$  values. Under the experimental conditions, some of the solvent acetone molecules will be protonated, and the relatively nucleophilic C5 atom within **1b** can then attack the electrophilic central acetone carbon. While compounds **1a**, **1c**, and **1d** have similarly basic C5 carbons, they may be too sterically crowded to undergo the same reaction. Interestingly, **1a** yields the ring opened triketone on heating with HCl (Scheme 2) while **1b** does not react under these conditions (Scheme 3). Whether this discrepancy in chemistry arises from differences in the position of initial protonation or the presence of a furan methyl group (or both) will be addressed in a forthcoming theoretical analysis of the reaction mechanism.

The terminal hydroxyl group in **1c** significantly influences the  $pK_a$  values within the furan ring. With the exception of C5 and the ketone oxygen, calculated  $pK_a$  values of the furan carbon atoms are *ca.* 1 to 3  $pK_a$  units less basic than in **1a**, with  $pK_a$  values ranging from  $-13.4$  to  $-19.4$ . Again, the calculated carbonyl  $pK_a$  goes from  $-18.1$  to  $2.0$  when SMD solvation and an explicit water molecule are used. The hydroxyl moiety of **1c** is not in resonance with the furan ring, and therefore inductively removes electron density from the ring system toward C5, whose calculated  $pK_a$  is  $-13.4$  versus  $-14.7$  in **1a**. This results in the more negative  $pK_a$  values for C2 through C4. The furan oxygen is also calculated to be more basic by 1.2  $pK_a$  units. Initial attempts to calculate a  $pK_a$  value for the hydroxyl group of **1c** were unsuccessful because protonation of the hydroxyl oxygen of **1c** yields an unstable structure, where the protonated hydroxyl group migrates to the C4 position during gas phase CBS-QB3 geometry optimization.<sup>19</sup> Addition of an explicit water molecule hydrogen bonded to the alcohol group with SMD solvation eliminates this problem, however, and a  $pK_a$  of 2.6 is calculated for the hydroxyl group. Both the carbonyl and hydroxyl oxygens of **1c** are thus the most basic<sup>33</sup> by a large margin, which is consistent with the dehydration shown in Scheme 5.

Reduction of the carbonyl of **1a** to yield **1d** makes the furyl ring more basic by 0.3–2.1  $pK_a$  units (Scheme 9). Initial calculations of the  $pK_a$  of the alcohol group of **1d** gave a value of  $-18.8$ . This again is very different from the relevant experimental value of  $-2$  for 2-butanol<sup>34</sup> Addition of just one explicit water molecule with SMD solvation gives a calculated value of 2.3. Therefore the most basic site of **1d** is the hydroxyl group.

A similar trend is found upon reduction of the carbonyl in **1b** to give **1e**: the furyl ring becomes more basic by 0.3–1.7  $pK_a$  units with the exception of C2 (less basic by 0.6  $pK_a$  units). In comparison to **1a** and **1b**, the furan ring of **1e** is less basic than that of **1d** by 1.6–5.6  $pK_a$  units with the exception of C5, which is more basic by 0.7  $pK_a$  units. Again, the  $pK_a$  of the hydroxyl group was initially calculated as  $-19.0$ , but rises to 2.3 when an explicit water molecule with SMD solvation is added, and is the most basic site of the molecule.

The  $\alpha,\beta$  unsaturated compounds possess significantly different  $pK_a$  values. The furan ring carbon atoms of **3a** have calculated

$pK_a$  values ranging from  $-17.3$  to  $-21.1$ , *i.e.* these are less basic than those of **1a** by approximately 3–5  $pK_a$  units. The furan ring oxygen atom is also less basic with a  $pK_a$  of  $-35.8$ , while the olefinic carbon center,  $\alpha$  to the ketone group has a  $pK_a$  value of  $-13.0$ . A  $pK_a$  value for the carbon atom  $\beta$  to the ketone moiety could not be calculated, as the proton on this carbon migrates across the double bond during geometry optimization.<sup>19</sup> Like **1a–e**, the calculated  $pK_a$  of the carbonyl oxygen in **3a** increases significantly from  $-10.5$  to 4.6 on inclusion of an explicit water molecule with SMD solvation. This is 4.2  $pK_a$  units more basic than the ketone oxygen atom of **1a** and illustrates the magnitude of the resonance stabilization provided by the enone moiety that is not available in **1a**.

As illustrated above, in going from **1a** to **1b**, replacement of the **3a** furyl methyl group with a proton to give **3b** significantly alters the calculated  $pK_a$  values. In the case of **3b**, the furan oxygen and C2–C4 sites are  $\sim 1$ –5  $pK_a$  units less basic than in **3a**, while C5 is 1.1 units more basic than in **3a**. The olefinic carbon  $\alpha$  to the ketone carbonyl is 4.2 units less basic than that of **3a**, with a  $pK_a$  of  $-17.2$ . As in **3a**, protonation at the  $\beta$  olefinic carbon resulted in migration across the double bond during geometry optimization, thus preventing calculation of the corresponding  $pK_a$  value. Here again the ketone oxygen is the most basic site in **3b** with a  $pK_a$  of  $-12.3$  that increases to 3.6 on inclusion of an explicit water molecule with SMD solvation, (*i.e.* 3.5 units more basic than in **1b**). That the ketone is the most basic site of **3a** and **3b** is consistent with an ion cyclotron resonance study of protonation of the structurally similar  $\alpha,\beta$  unsaturated ketones 3-penten-2-one and 3-methyl-3-buten-2-one, in which the ketone-protonated analogues were found to be the most stable.<sup>35</sup>

As in **1c**, the inductive effect of the electron withdrawing hydroxyl group within **3c** makes the C2–C4 carbon atoms of the furan ring comparatively less basic (with  $pK_a$  values ranging from  $-19.5$  to  $-22.9$ ). The C5 carbon atom is again more basic by  $\sim 1$   $pK_a$  unit ( $-16.2$ ) while the furan oxygen  $pK_a$  is identical to that of **3a** ( $-35.8$ ). The carbon atom  $\alpha$  to the ketone group is less basic than that in **3a** ( $pK_a$  of  $-14.2$ ), and protonation at the  $\beta$  position once again results in migration across the double bond during optimization. More importantly, as in **1c**, protonation at the **3c** hydroxyl group yields an unstable structure that undergoes water molecule migration during gas phase CBS-QB3 geometry optimization.<sup>19</sup> Again, as in the case of **1c**, addition of an explicit water molecule hydrogen bonded to the hydroxyl group gives stable structures, and enables calculation of a  $pK_a$  of  $-6.6$  for the hydroxyl group of **3c**.<sup>19</sup> This value increases to 0.2 when SMD solvation is used. Thus, as for **1c**, the hydroxyl group is the most basic site of **3c**. The ketone oxygen is the next most basic atom within **3c**, with a calculated  $pK_a$  of  $-12.5$  with an explicit water molecule added which increases to 3.6 with SMD solvation.

## Discussion

Heating **1a** simply with 10 mol% hydrochloric acid as catalyst at only 80–100 °C, in air leads to furan ring opening and a single product, **2a** (Scheme 2). Under these mild conditions compound **1d** is ring opened cleanly to **2d** (Scheme 6) while **1b** and **1c** yield more complicated product mixtures (Schemes 3,4 and 5), as

discussed below. Strong Brønsted acids work well as catalysts, while weaker Brønsted acids are much less effective. Studies of the ring opening of **1a** in buffered solution indicate a specific acid catalysis mechanism, and this mechanism is also likely where ring opening is observed in other substrates tested here (e.g. **1d**).

The reaction solvent system also has a significant effect on the yield of the reaction, as evidenced by the test of various solvent systems using **1a** shown in Table 1. The solubility of **1a** was greatly improved in all of the mixtures of water and water-miscible organic solvent tested. This improved solubility did not necessarily lead to more product, however: pure water and a 1 : 1 mixture of water and methanol gave equivalent yields (86% vs. 87%) of **2a** over 24 hours. Acetonitrile:water mixtures worked almost as well, giving **2a** in 77% yield. In contrast, acetone, ethanol and isopropanol all gave significantly lower yields of **2a**. Addition of an organic co-solvent is known to cause changes in ion dissociation and substrate  $pK_a$  values<sup>36</sup> as well as leading to preferential solvation.<sup>37</sup> The concentration of reactant water is also decreased, which may slow the reaction.

Some recent computational studies have examined various chemical transformations of biomass derivatives to chemical feedstocks,<sup>38</sup> but none have examined the ring opening of furans within these classes of compounds in detail.<sup>39</sup> As illustrated in Table 3, DFT calculations carried out at the 6-311+G(d) level indicate that ring opening of **1a–e** to the corresponding products **2a**, **2b\***, **2c–e** is downhill by 2.03 to 4.92 kcal mol<sup>−1</sup>. The CBS-QB3 results indicate that ring opening is slightly endergonic, by 0.28 to 3.45 kcal mol<sup>−1</sup>. In either case, the reaction will be further pushed towards product formation by the high concentrations of water present under the reaction conditions. The diverse reactivities of **1a–1e** under similar conditions, however, (ring opening for **1a** and **1d** (Schemes 2 and 6), slight decomposition for **1b** and **1e** (Schemes 4 and 7), and decomposition to **3a** for **1c**) (Scheme 5) indicate that the kinetic pathways of these reactions are important in determining the observed products.

That the  $\alpha,\beta$  unsaturated compounds (**3a–3c**) are unreactive toward ring opening (Scheme 8) is supported by both levels of theory: the overall reaction is calculated to be more uphill than in the case of their corresponding saturated counterparts (**1a–c**). For **3a** and **3b**, upon initial protonation at the carbonyl, both the rigidity of the butenone side chain due to enhanced  $\pi$ -conjugation and the poor basicities of the C2 positions should inhibit proton transfer to the furan ring and hence ring opening (Scheme 8).

The  $pK_a$  values calculated for **1a** and **1b** (Scheme 9) indicate that they are poor bases, and that the most basic site is the ketone oxygen. Because proton transfer does not occur in the rate limiting step, the most basic site in each substrate is not the sole influence in determining which products are observed during a specific acid catalysis mechanism. Consideration of  $pK_a$  values is instructive here however, as the  $pK_a$  values determine the pre-equilibrium species that form. Upon carbonyl protonation, the butanone side chain of **1a** may be able to approach and protonate the furan C2, possibly through a water-assisted transition state,<sup>40</sup> and begin the observed ring opening mechanism. Alternatively, the species formed upon protonation

of the ketone oxygen may be unreactive in terms of ring opening, and enough protonation at the furan ring occurs in solution for the reaction to occur. Indeed, protonation of the furyl C2 or C5 site is consistent with both experimental and theoretical work on furan and methyl furans.<sup>41</sup> Either way, protonation of the ring of **1a** could then be followed by nucleophilic attack of water leading to the ring opened triketone **2a**; a theoretical study of the mechanism of this process is currently underway.

Furfural and HMF represent major components of biomass<sup>4,5,42</sup> and therefore are promising precursors for biofuels. Accordingly, compound **1b** is synthesized using furfural while **1c** is synthesized using HMF. In contrast to the reactions of **1a** that yielded only one product (Scheme 2), reactions of **1b** and **1c** were more complex (Schemes 3, 4 and 5). Here, consideration of  $pK_a$  values may be more instructive, because for reactions where ring opening is not observed the rate limiting step is likely different. For **1b**, the 19 carbon product **2b** is obtained cleanly when heated in 1 : 1 water : acetone with HCl as a catalyst (Scheme 4). Compound **2b** is the product of condensation of two molecules of **1b** and one acetone molecule, and similar reactions have been reported using stoichiometric and catalytic amounts of acid as well as metal catalysts.<sup>43</sup> Slight decomposition of **1b** is observed in other solvent mixtures, and no significant ring opening is observed. The furyl C2 position of **1b** is comparatively less basic than in **1a** ( $pK_a$ : −13.0 (**1b**) vs. −17.0 (**1a**)), which may prevent a water assisted proton transfer from the ketone oxygen to C2, thereby preventing ring opening.

The reactivity of **1c** is also more complicated. When heated in the presence of acid catalyst, the major product is the  $\alpha,\beta$  unsaturated compound **3a** (Scheme 5), which forms *via* acid catalyzed dehydration. Calculation of an accurate  $pK_a$  value for the protonated alcohol moiety of **1c** required inclusion of an explicit water molecule in addition to the solvent continuum. The resulting  $pK_a$  calculations show that the alcohol group is the most basic site of the molecule by 0.6  $pK_a$  units.<sup>44</sup> The proximity of the alcohol group to the furan ring  $\pi$ -electrons thus apparently lowers the barrier for dehydration significantly. Furthermore, the thermodynamic calculations indicate that this dehydration reaction is quite downhill: going from **1c** to **3a** with release of H<sub>2</sub>O has a  $\Delta G^\circ$  of −15.0 kcal mol<sup>−1</sup> at the CPCM/B3LPY/6-311+G(d) level of theory and a  $\Delta G^\circ$  of −10.2 kcal mol<sup>−1</sup> at the CPCM/CBS-QB3 level of theory. The  $\alpha,\beta$  unsaturated compounds are unreactive under our experimental conditions, so this dehydration reaction substantially limits the yield of ring opened products. In terms of biofuels production, any **3a** formed could be recovered, the olefin reduced to give **1a**, which could then be ring opened. These purification and hydrogenation steps could add prohibitive costs however, and an alternative would be to dehydrate any HMF to methylfurfural<sup>45</sup> for synthesis of **1a**. The other products formed in this reaction were not identified, but <sup>1</sup>H NMR spectra indicate that some ring opening does occur. These differences in products and selectivities among **1a–c** under the same conditions highlight the sensitivity of the ring opening chemistry to the nature of the substrate.

That compound **1d** ring opens cleanly to **2d** (Scheme 6) while **1e** decomposes slightly under the same conditions (Scheme 7) is interesting. The exact same trend is seen for **1a**

(Scheme 2) and **1b** (Scheme 3), respectively. Furthermore, the computed  $pK_a$ s with SMD solvation and explicit water molecules of the protonated carbonyl groups of **1a** and **1b** (0.4 and 0.1, respectively) are similar to those of the hydroxyl groups in **1d** and **1e** (both 2.3). Thus, the reaction pathways analogous to those postulated above for **1a** and **1b** should apply to substrates **1d** and **1e** as well. Despite the comparatively basic hydroxyl groups of **1d** and **1e**, no alcohol dehydration products are observed, in contrast to **1c**. Acid catalyzed dehydration of secondary alcohols typically requires concentrated sulfuric or phosphoric acid and higher temperatures. In contrast to the dehydration of the primary alcohol in **1c** (Scheme 5), the lack of dehydration of the secondary alcohols in **1d** and **1e** under the same conditions (Schemes 6 and 7) is likely due to the lack of  $\pi$ -electrons available to stabilize intermediates of dehydration of **1d** or **1e**.

Finally, calculated  $pK_a$  values proved very instructive in this study, and the success of these calculations, which are notoriously difficult,<sup>46</sup> rested on two things. First, calibration of the calculated values against the experimentally measured  $pK_a$  of 2,5 di-*tert*-butylfuran using various methods for solvation free energies ensured that accurate and thereby chemically intuitive  $pK_a$  values were obtained. Second, use of explicit hydrogen-bonded water molecules along with SMD solvation free energies proved critical for protonation of alcohol and ketone moieties. A few studies have shown that inclusion of one or more explicit solvent molecules can greatly increase the accuracy of  $pK_a$  calculations.<sup>47</sup> In the case of **1c** and **3c**,  $pK_a$  values for hydroxyl groups could not be calculated at all without inclusion of an explicit water molecule. For **1d** and **1e**, the calculated  $pK_a$  changed 11.0 and 10.6 units, respectively, upon addition of an explicit water molecule with SMD solvation. For the carbonyl groups of **1a–1c**, use of an explicit water molecule improved the  $pK_a$ s by 8.7–11.2 units.

Even better agreement of the calculated  $pK_a$ s with experimental values may be possible by including additional explicit water molecules, but this would lead to a drastic increase in complexity due to the number of molecular conformations as water molecules are added.<sup>48</sup> These results highlight that while polarizable continuum solvent models may approximate the overall polarity of a given solvent, they cannot account for stabilization due to specific solvent interactions, especially hydrogen bonding. Hydrogen bond strengths are on the order of 4 kcal mol<sup>-1</sup>,<sup>49</sup> and in aqueous acidic solution alcohol-water proton exchange can be significant.<sup>50</sup> A recent study found that inclusion of an explicit water molecule was not necessary for accurate calculation of  $pK_a$  values of cationic carbon acids if the charge on the carbon is sufficiently delocalized.<sup>49</sup> This is consistent with the results observed here: when calculating  $pK_a$  values for protonation of the furan ring of the substrates studied here, the furan  $\pi$  system helps delocalize the resulting positive charge and no explicit water molecules are required. No delocalization of charge is available to the alcohol moieties of **1d** and **1e** and carbonyl moieties of **1a–1c**, making the effects of hydrogen bonding more important.

For protonated carbonyl and hydroxyl groups with explicit hydrogen bonded water molecules, replacing CPCM with SMD/HF/6-31G(d) solvation free energies in the thermochemical cycle

improves the computed  $pK_a$ s significantly. Indeed, the  $pK_a$ s of the protonated alcohol groups in **1c**, **1d**, **1e**, and **3c** become 2.6, 2.3, 2.3, and 0.2, respectively, much closer to the experimental  $pK_a$  of  $-2$  for 2-butanol.<sup>33</sup> In addition, the range  $pK_a$ s for the protonated carbonyl groups of each substrate becomes 0.1–4.6, which is also in better agreement with the experimental value for acetone ( $-2$  to  $-3$ ).<sup>31</sup> One of the factors responsible for the superior performance of SMD over CPCM in computing  $pK_a$ s of protonated alcohol and carbonyl groups (in contrast to furan carbons) is likely the inclusion of such species (such as protonated acetone/acetophenone and protonated methanol/ethanol, each with an explicit hydrogen bonded water) in the SMD training set.<sup>30,51</sup>

## Conclusions

Furan rings contained within biomass-derived substrates can be ring opened under relatively mild conditions using simple, homogeneous Brønsted acid catalysts. Substituents on the furan rings can significantly alter the pathways of these proton catalyzed reactions. DFT calculations, aided by calibration to empirical values and inclusion of explicit water molecules when appropriate, support the notion that the location of initial protonation influences the products obtained. Compound **1a**, containing a methyl group in the 4-position of the furan ring, gives one product in excellent yield *via* protonation of the furan ring and subsequent nucleophilic attack of a water molecule. When heated in an acetone:water mixture, compound **1b** condenses with an acetone molecule and another molecule of **1b** to give the nineteen carbon compound **2b**. Only slight decomposition is observed when other solvent systems are used. The alcohol group within **1c** is relatively basic, and prone to dehydration to yield the unreactive  $\alpha,\beta$  unsaturated compound **3c** and other unidentified products.

In contrast to the more typical high temperature, high pressure heterogeneous conditions used in the processing of biomass, these studies demonstrate that simple homogeneous catalysts can be effective under milder conditions and can also confer excellent selectivities. Despite much recent interest in biorenewables, there has been relatively little effort focused on understanding the intimate details of the chemistry required to produce fuels from biomass. This study improves the understanding of such processes, and may enable the design of better catalysts and processes for transformation of biomass to fuels and commodity chemicals on large scales.

## Experimental section

Reagent grade chemicals and solvents were obtained from Aldrich, Acros or Fisher Scientific and used as received. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer at ambient temperatures and are referenced to a residual solvent peak. GC-MS analysis was obtained using a Hewlett-Packard 6890 GC system equipped with a Hewlett-Packard 5973 mass selective detector.

Compound **3a** was obtained *via* a room temperature morpholine trifluoroacetate catalyzed aldol condensation of acetone and 5-methylfurfural,<sup>16</sup> Similarly, compounds **3b** and **3c** were obtained *via* a room temperature, piperidine-catalyzed



aldol condensation between acetone and furfural or hydroxymethylfurfural, respectively.<sup>16</sup> Catalyst screening and ring opening reactions were performed in NMR tubes with 10  $\mu$ L of substrate (.066 mmol) in 400  $\mu$ L of solvent with 10 mol% catalyst added and the tubes were heated in a temperature controlled heating block. After heating, reaction mixtures were extracted three times with methylene chloride and the solvent removed *in vacuo*. The resulting residue was dissolved in  $\text{CDCl}_3$ , and a  $^1\text{H}$  NMR spectrum was recorded with a delay time of 10 seconds to insure accurate integrals. Peak areas were calculated using the MestReNova line fitting tool.<sup>52</sup>

#### Synthesis of 4-(5-methyl-2-furyl)-2-butanone (1a)

Compound **3a** (5.95 g, 36.6 mmol) was reduced using magnesium in a methanol/THF mixture<sup>17</sup> and purified by silica gel chromatography using 90:10 hexanes: $\text{Et}_2\text{O}$  as eluent. Yields 4.64 grams (77%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.16 (s, 3H,  $\text{COCH}_3$ ), 2.23 (s, 3H, furan  $\text{CH}_3$ ), 2.76 (t, 2H,  $\text{CH}_2$ ), 2.85 (t, 2H,  $\text{CH}_2$ ), 5.83 (d, 1H,  $\text{CH}$ ), 5.85 (d, 1H,  $\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  13.60, 22.43, 30.04, 42.07, 105.92, 106.05, 150.70, 152.77, 207.60.

#### 4-(2-Furanyl)-2-butanone (1b)

Prepared analogously to **1a** from **3b** (0.206 g, 1.51 mmol) and purified by silica gel chromatography using methylene chloride as eluent. Yields 0.194 grams (93%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.16 (s, 3H,  $\text{CH}_3$ ), 2.78 (t, 2H,  $\text{CH}_2$ ), 2.91 (t, 2H,  $\text{CH}_2$ ), 5.99 (m, 1H,  $\text{CH}$ ), 6.27 (m, 1H,  $\text{CH}$ ), 7.29 (m, 1H,  $\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 22.27, 29.37, 29.99, 41.78, 105.29, 110.31, 141.18, 207.39.

#### 4-(5-Hydroxymethyl)-2-furanyl-2-butanone (1c)

Prepared analogously to **1a** from **3c** (0.198 g, 1.19 mmol) and purified by silica gel chromatography using  $\text{Et}_2\text{O}$  as eluent. Yields 0.138 grams (69%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.17 (s, 3H,  $\text{CH}_3$ ), 2.79 (t, 2H,  $\text{CH}_2$ ), 2.90 (t, 2H,  $\text{CH}_2$ ), 4.55 (s, 2H,  $\text{CH}_2\text{OH}$ ), 5.94 (d, 1H,  $\text{CH}$ ), 6.17 (d, 1H,  $\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  22.37, 30.04, 41.75, 57.64, 106.18, 108.78, 152.71, 154.91, 207.41.

#### Synthesis of 4-(5-methylfuran-2-yl)butan-2-ol (1d)

A vial was filled with 5 mL of absolute ethanol and 50  $\mu$ L of **1a** (0.332 mmol). To this, 45 mg of  $\text{NaBH}_4$  (1.18 mmol) was added and the solution was stirred for half an hour, followed by workup with dilute HCl, extraction with methylene chloride and removal of solvent *in vacuo* to yield **1d**. Yields 0.047 grams (94%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.22 (d, 3H,  $\text{CHCH}_3$ ), 1.76 (m, 2H,  $\text{CH}_2$ ), 2.25 (s, 3H, furan  $\text{CH}_3$ ), 2.68 (m, 2H,  $\text{CH}_2$ ), 3.84 (m, 1H,  $\text{CH}$ ), 5.84 (m, 1H,  $\text{CH}$ ), 5.86 (m, 1H,  $\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  13.65, 23.64, 24.59, 37.69, 67.60, 105.65, 105.97, 150.54, 154.03.

#### Synthesis of 4-(furan-2-yl)butan-2-ol (1e)

Prepared analogously to **1d** from **1b** (0.0567 g, 0.41 mmol) and purified through a silica plug using methylene chloride as eluent. Yields 0.042 g (73%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.23 (d, 3H,  $\text{CHCH}_3$ ), 1.79 (m, 2H,  $\text{CH}_2$ ), 2.74 (m, 2H,  $\text{CH}_2$ ), 3.84 (m, 1H,  $\text{CH}$ ), 6.00 (d, 1H, furan  $\text{CH}$ ), 6.28 (d, 1H, furan  $\text{CH}$ ), 7.3 (7.30, 1H, furan  $\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  23.63, 24.48, 37.50, 67.46, 105.01, 110.26, 141.03, 155.91.

#### Synthesis of 2b

**1b** (0.010 g, 0.032 mmol) was heated at 80  $^\circ\text{C}$  for 24 hours in a 1:1 by volume mixture of water and acetone with 10 mol% HCl added. After heating, the reaction mixture was extracted three times with methylene chloride, dried over  $\text{MgSO}_4$ , and the solvent removed to give **2b** in 92% yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.56 (s, 6H,  $\text{CCH}_3$ ), 2.14 (s, 6H,  $\text{COCH}_3$ ), 2.73 (t, 4H,  $\text{CH}_2$ ), 2.86 (t, 4H,  $\text{CH}_2$ ), 5.84 (m, 2H,  $\text{CH}$ ), 5.86 (m, 2H,  $\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  22.60, 26.45, 30.06, 37.44, 41.88, 104.61, 105.62, 153.01, 158.87, 207.64.

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